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EDITORIAL COMMENT

The Search for Myocardial Protection

Is There Still Hope?*

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There are few pursuits in medicine that have yielded so little from so much effort as the search for myocardial protection therapies, which began in earnest over 30 years ago (1). The search has been warranted because ischemic heart disease is growing as the world's leading cause of death and disability. New therapy for the acute manifestation of myocardial infarction aimed at reducing myocardial damage and improving clinical outcomes is a high priority.

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What is known about myocardial protection? Ischemic preconditioning is an important physiological mechanism, is mediated in part through adenosine and protein kinase C activation (2), and likely explains some of the heterogeneity in patient outcomes with acute myocardial infarction. Dozens of treatments reduce infarct size in animal models of ischemia-reperfusion. However, the relevance of most of these animal models to human acute myocardial infarction is questionable (3). Generally, when tested in humans, treatments effective in experimental models have not been shown to reduce infarct size. The concept of providing complementary clinical benefit to reperfusion therapy, however, is well founded. Angiotensin-converting enzyme inhibitors provide an example of a therapy that improves outcome in the early hours and days after acute myocardial infarction (MI), 40% of the early survival benefit occurring on the first day of treatment (4), in part through modifying ventricular remodeling.

Is there any hope for myocardial protection based on clinical trial results? In humans, some therapies do seem to reduce myocardial damage in the ischemia-reperfusion setting, including adenosine in acute myocardial infarction (5,6) and cariporide in coronary artery bypass surgery (7). This is important because it provides support to the concept that myocardial protection can be accomplished in the clinical setting. However, the benefits so far have either not been large enough to warrant further clinical development or have been counterbalanced by adverse effects (7).

The care of acute myocardial infarction was transformed by reperfusion therapy, which established the relationship between faster, more complete myocardial perfusion and improved survival. But reperfusion therapy, both in animal models and in clinical trials, comes at a cost, with an early hazard that is not completely explained by bleeding complications (8). A variety of approaches have been tried to overcome "reperfusion injury" and protect the myocardium, including inhibiting the inflammatory response, modifying harmful intracellular calcium influx, stabilizing membranes, reducing apoptosis, enhancing metabolic pathways to provide resistance to ischemic damage, improving energy metabolism, inducing therapeutic hypothermia, and improving oxygen delivery. Several of these approaches have been aimed at improving microvascular function, which may be especially important with primary percutaneous coronary intervention (PCI) where the epicardial artery is effectively opened in the vast majority of cases, but tissue-level perfusion may be incomplete.

Aqueous oxygen is intended to improve myocardial oxygen delivery and microvascular function. Initial experiments in animal models of reperfusion of myocardial infarction showed that aqueous oxygen had beneficial effects on both ventricular function and microvascular blood flow as measured by radiolabeled microspheres (9). Additionally, small clinical pilot studies suggested that aqueous oxygen may prevent adverse remodeling and improve ventricular function (10,11).

In this issue of the *Journal*, O'Neill et al. (12) report a multicenter randomized trial of 269 patients undergoing primary or rescue PCI within 24 h of symptom onset evaluating hyperoxemic reperfusion with aqueous oxygen. Importantly, patients with normal epicardial flow at the time of initial infarct angiography (Thrombolysis In Myocardial Infarction flow grade 3 before intervention) were excluded. Patients were randomized after successful PCI to receive aqueous oxygen (TherOx Inc., Irvine, California) delivered through a novel system that mixes oxygen with blood, achieving a pO_2 of 760 to 1,000 mm Hg, or normoxemic blood autoreperfusion, delivered into the proximal portion of the infarct-related artery. Each patient had a comprehensive and complementary array of evaluations, including continuous ST-segment monitoring; serial contrast echocardiography at 24 h, 1 month, and 3 months; and infarct size as measured by ^{99m}Tc-sestamibi single-photon emission computed tomography imaging at 14 to 21 days. Intracoronary hyperoxemic reperfusion did not improve

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regional wall motion, ST-segment resolution, or final infarct size. In a post-hoc analysis, there was improved regional function in patients with anterior MIs treated within 6 h of symptom onset.

The trial team successfully completed a rigorous and challenging clinical trial. The trial did not show a benefit of hyperoxemic reperfusion in acute MI. When such a trial shows no benefit in the overall population, subgroup findings are hypothesis-generating only. Whether aqueous oxygen treatment is ineffective or whether there was some benefit that was either not detected or was present in certain subpopulations is not known. What lessons can be learned for future research?

The negative findings are not surprising, and this study reinforces the pattern of negative clinical studies of myocardial protection. It is likely that failure to replicate experimental data in clinical trials relates, at least in part, to the lack of relevance of the highly controlled ischemia and reperfusion in animal models compared with the more complex reperfusion that occurs in patients. The choice of patient population may be crucial in evaluation of myocardial protection. Agents directed toward improving the myocardial reperfusion itself are time-limited to the period known to define when myocardial salvage occurs (i.e., the first 3 to 6 h). Thus, limiting acute inflammatory damage to improve microvascular function might be most effective in patients presenting relatively early after symptom onset and with large (anterior) myocardial infarctions. Several clinical trials have suggested more benefit in anterior than inferior MI location (6,12,13) and in earlier-presenting patients (12,14). Studying patients with large infarctions, and perhaps anterior MI in particular, makes sense because these are higher-risk patients in most need of better therapy. Focusing on the very early presenters creates a paradox, however—the earliest-presenting patients have such good outcomes that it will be difficult to show incremental value. In contrast to what was accomplished in this study, initiating the therapy as early as possible (and before reperfusion) may be important, although complex delivery needs may limit the practical application of therapies such as aqueous oxygen. As the investigators acknowledge, in this study the inclusion of patients with symptoms up to 24 h may have limited the ability to show a treatment difference. It is plausible, and a reasonable hypothesis for further study, that the subset of patients with anterior MI of <6 h is the population most likely to benefit.

On the other hand, treatment intended to prevent apoptosis, to modify remodeling, and to enhance regeneration might provide benefits to patients with longer delays to reperfusion. A complicating factor is that the exact mechanism of benefit, if present, is not known for many potential myocardial protection therapies.

Another possibility is that the methods for detecting relevant reductions in infarct size in phase II trials of myocardial protection have simply been too insensitive. The exploratory multimarker analysis used in the present study has been the best approach to guide whether there is sufficient probability of success to proceed to clinical outcomes trials. Another tool, delayed enhancement imaging with cardiac magnetic resonance (CMR), seems to be ready for use in multicenter trials. Studies comparing delayed-enhancement CMR with single-photon emission computed tomography have shown higher resolution for smaller (often subendocardial) infarctions (15). The resolution of CMR also allows evaluation of the transmural extent of infarction and that relates to subsequent improvement in myocardial function (16). Finally, CMR allows visualization of areas of microvascular obstruction in necrotic and perinecrotic regions (17,18). Cardiac magnetic resonance has been performed in both animal models and in multicenter clinical trials (19) evaluating myocardial protection. In a multicenter study of cell therapy (20), CMR was able to detect small improvements in global and regional left ventricular function.

Is the continued search for myocardial protection a stubborn exercise in futility, or an elusive opportunity to eventually improve patient care? Although any individual therapy has a high risk for failure, the likelihood is that with improved understanding and refined clinical development programs, selected approaches to myocardial protection will eventually succeed.

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